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US 4778677 A US 20010055645 A1  
WPI Abstract Accession No 2001-406520/43 &  
RU002167655 (M.G. CHUKHROVA ET AL)**

(58) Field of Search

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(54) Abstract Title

**Pharmaceutical composition and method to alleviate withdrawal symptoms and balance nutritional deficiency brought about by caffeine abuse**

(57) Method and compositions for effecting withdrawal symptoms and balancing of nutritional deficiency, which developed due to the caffeine abuse, and aiding in the gradual cessation or lessening of caffeine use or abuse. The pharmaceutical compositions are comprised of a therapeutically effective combination of caffeine with nutritional supplementation of vitamins and/or minerals and a pharmaceutically acceptable carrier inert or physiologically active. According to another aspect of the invention it is directed to the correction of the nutritional deficiencies, which exist due to individual's chronic caffeine intake and plays an important part in the withdrawal syndrome. One or more vitamins and/or one or more minerals, chemical or natural in origin, may be used in the composition of the invention.

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**Method and compositions for effecting withdrawal symptoms and balancing of nutritional deficiency, which developed due to the caffeine abuse.**

The invention relates to the use of caffeine, caffeine derivatives or a pharmaceutically acceptable salts thereof for manufacture of medicaments or nutritional supplements effective for the reduction of caffeine withdrawal symptoms, developed due to chronic overdose of drinks, food or drugs, which contains caffeine, and aiding in the gradual cessation or lessening of caffeine use or abuse. The pharmaceutical compositions are comprised of a therapeutically effective combination of caffeine with nutritional supplementation of vitamins and/or minerals and a pharmaceutically acceptable carrier. The method of preparing and using these compounds is also disclosed.

#### **Field of the invention**

This invention relates to compositions comprising caffeine and methods to prepare said compositions for manufacture of medicaments or nutritional supplements useful in drug therapy, preferably caffeine substitution or replacement of caffeine and caffeine intake, gradual cessation with balancing of nutritional deficiency, which developed due to individual caffeine abuse.

## Background of the invention

Caffeine (1,3,7-trimethylxanthine) is the most widely used physiologically active substance in the world and has been considered as a legal drug of abuse: [url.http://www.a1b2c3.com/drugs/gen007.htm](http://www.a1b2c3.com/drugs/gen007.htm), National Institute on Drug Abuse rating.

Most of the caffeine consumed comes from dietary sources such as coffee, tea, cola drinks, and chocolate. Caffeine is also present in many non-prescription medications, such as cold remedies, analgesics, and weight loss products. Moderate caffeine consumption, less than 300 mg/day, very rarely leads to health risks. Higher doses of caffeine, 500 mg/day and more induce negative effects that include anxiety, restlessness, insomnia, and tachycardia; these effects are seen primarily in a small subset of individuals, who developed caffeine tolerance. Also caffeine was described as a potential drug of abuse, and in a more recent article as "a model drug of abuse."

Individual caffeine consumption from all sources can be estimated as 76 mg/day worldwide but reaches 210-240 mg/day in the United States and Canada and >400 mg/day in Sweden and Finland, where 80-100% of caffeine intake comes from coffee alone: Debry, G. Coffee and Health; John Libbey: Paris, 1994. Over half the population of the United States drinks at least two cups of coffee a day. 25% of coffee drinkers consume about five cups daily, and another 25% drink ten or more cups a day.

In the United Kingdom, the consumption is as high as in Sweden and Finland, but 72% is consumed as tea. According to one survey, the daily intake of caffeine from all sources in the United States amounts to 2.4-4.0 mg/kg body wt or 170-300 mg in a 60-70 kg-individual. In individuals older than 10 years old, two-thirds of this amount comes from coffee. In children, soft drinks represent 55% of the total caffeine intake, chocolate foods and beverages 35-40%, and tea 6-10%: Ellison, C. R.; Singer, M. R.; Moore, L. L.; Nguyen, U.S.D.T.; Garrahe, E.; Maror, J. K. Journal of the American Dietetic Association. 1995, 95, 802-804.

Also caffeine, as a central nervous system stimulator, presents many positive effects: reducing drowsiness, gives well-being feeling, stimulates brain and behaviour, increases the basal metabolic rate, improved short term high intensity exercise tolerance, stimulates vascular system, improve short-term memory etc: Does caffeine lead to psychological dependence? by Astrid Nehlig CHEMTECH July 1999 CHEMTECH 1999, 29(7), 30-35. But extensive caffeine use may produce tolerance, dependency, intoxication, withdrawal symptoms and also metabolism disturbances such as: hypoglycaemia, increases plasma epinephrine and homocysteine levels, mineral depletion, exhausted adrenals, increases lost of calcium, potassium, magnesium, iron, trace minerals and vitamins, especially thiamine.

A large percentage of the population may experience withdrawal symptoms following sudden cessation of caffeine consumption, while gradual cessation over 2-3 days has not been shown to result in such symptoms. Even persons who consume low or moderate amounts of caffeine may have a withdrawal syndrome after their daily consumption of caffeine ceases. Withdrawals symptoms generally begin 12-24 h after sudden cessation of caffeine consumption and reach a peak after 20-48 h. Withdrawal symptoms are: craving for coffee, headache, irritability, insomnia, fatigue, depression, apathy, constipation, anxiety, shakiness, dizziness, inability to concentrate, nausea, cramps, tachycardia.

Various pharmacological approaches for treating caffeine withdrawal symptoms have been tried (US5219858, US5152994, US5051426), each has

presented certain limitations and drawbacks. For example: withdrawal symptoms may be only minimally relieved, and this may lead to enhanced craving for the caffeine. Or, individual may create an addiction for the 'substituted' drug, in substitution therapy. None of these approaches include the balancing of the nutritional deficiency which developing due to individual caffeine abuse and plays an important part in the withdrawal syndrome.

Thus, a very substantial need in the art exist for a methods and compositions for the reduction of caffeine withdrawal symptoms, developed due to overdose of drinks, food or drugs, which contains caffeine, and aiding in the gradual cessation or lessening of caffeine use or abuse.

## Summary of the invention

The invention provides a pharmaceutical compositions for the palliation of caffeine withdrawal symptoms, developed due to overdose of drinks, food or drugs, which contains caffeine; and aiding in the gradual cessation or lessening of coffee use or substance abuse. The pharmaceutical compositions are comprised of a therapeutically effective combination of caffeine with nutritional supplementation of vitamins and/or minerals and a pharmaceutically acceptable carrier inert or physiologically active. Said compositions, comprising caffeine with one or more vitamins and/or minerals, chemical or natural in origin, help gradually reduce and discontinue caffeine use and to control nutritional deficiency, which developed due to chronic caffeine intake. The invention is a unique composition by means of which permits caffeine replacement therapy to be effective and convenient.

According to another aspect of the invention it is directed to the correction of the nutritional deficiencies, which exist due to individual's chronic caffeine intake and plays an important part in the withdrawal syndrome. One or more vitamins and/or one or more minerals chemical or natural in origin advised to be used in the composition.

In more specific embodiment of the invention, the caffeine is used as Caffeine Citrate or other pharmaceutically acceptable salts of caffeine.

Vitamins are selected from: Bioflavonoids, Biotin, Choline, Folic acid, Inositol, Vitamin A, Vitamin B1, Vitamin B2, Vitamin B3, Vitamin B5, Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, Vitamin K.

Minerals are selected from: Aluminium (Al), Antimony (Sb), Arsenic (As), Barium (Ba), Beryllium (Be), Bismuth (Bi), Boron (B), Bromine (Br), Cadmium (Cd), Calcium (Ca), Caesium (Cs), Chloride (Cl), Chromium (Cr), Cobalt (Co), Copper (Cu), Cyanide (Cn), Fluoride (Fl), Gallium (Ga), Germanium (Ge), Gold (Au), Indium (In), Iodine (I), Iron (Fe), Lead (Pb), Lithium (Li), Magnesium (Mg), Manganese (Mn), Molybdenum (Mo), Nickel (Ni), Niobium (Nb), Phosphorus (P), Platinum (Pt), Potassium (K), Rubidium (Rb), Scandium (Sc), Selenium (Se), Silicon (Si), Silver (Ag), Sodium (Na), Strontium (Sr), Sulfur (S), Tellurium (Te), Thallium (Tl), Tin (Sn), Titanium (Ti), Tungsten (W), Vanadium (V), Zinc (Zn), Zirconium (Zr). The preferable natural source of minerals and trace elements is mumijo: natural resin.

Pharmaceutically acceptable carrier may be inert or physiologically active.

### Utility and Mode of administration:

The compositions are, furthermore, applicable for, but not restricted to, oral or nasal, buccal, pulmonary, transdermal and rectal routes of administration. Suitable, but not limiting administration forms are nasal or oral sprays, buccal sprays, chewing gums, tablets, lozenges, transdermal or buccal patches, nasal gels, transdermal or buccal gels, transdermal or buccal adhesives, or sprays or aerosols for administration to the lungs. The preferable administration forms are nasal or oral sprays or transdermal patches, as caffeine, vitamins and minerals delivery then avoids the hepatic first-pass effect and may be used in smaller doses.

The doses depend on the effect sought, the treatment period and the administration route used, they are generally for caffeine between 10 - 300 mg/ daily for an adult and according to the Recommended Daily Allowance (RDA) for vitamins and/or minerals. In order to be effective, compositions must be administered at times when a person experiences any withdrawal symptoms. Withdrawal symptoms are: craving for coffee, headache, irritability, insomnia, fatigue, depression, apathy,

constipation, anxiety, shakiness, dizziness, inability to concentrate, nausea, cramps, tachycardia.

### **Detailed description of the invention**

The invention relates to the use of caffeine or pharmaceutically acceptable salts thereof for manufacture of medicaments or nutritional supplements effective for the reduction of caffeine withdrawal symptoms, developed due to overdose of drinks, food or drugs, which contains caffeine, and aiding in the gradual cessation or lessening of coffee use or substance abuse. The pharmaceutical compositions are comprised of a therapeutically effective combination of caffeine with nutritional supplementation of vitamins and/or minerals and a pharmaceutically acceptable carrier.

In more specific embodiment of the invention, the caffeine is used as Caffeine Citrate, Caffeine Anhydrous or other pharmaceutically acceptable salts of caffeine. In order to be effective, caffeine must be administered at times when a person experience any withdrawal symptoms, such as: craving, depression, apathy, anxiety, fatigue, drowsiness, inability to concentrate, etc. Oral administration of caffeine in drink or tablet form provides rapid assimilation of the caffeine into the central nervous system and therefore rapid palliation of the withdrawal symptoms. In the present invention recommended form of administration are nasal or oral sprays, and then smaller amount of caffeine provides more rapid palliation of the withdrawal symptoms. The recommended safe daily quantity of caffeine, which can be administered to an adult without risk of developing withdrawal symptoms, is less than 300 mg/day, with no more than 100 mg per individual dose. Available on the market nasal or oral delivery systems may deliver a standard dose volumes 0.045- 1 ml therefore we recommend caffeine 10 - 100 mg per individual dose with no more than 300 mg/day.

The compositions are unique as they help not only gradually reduce and discontinue caffeine but also to control nutritional deficiency, which developed due to the chronic caffeine intake.

Vitamins are selected from: Bioflavonoids, Biotin, Choline, Folic acid, Inositol, Vitamin A, Vitamin B1, Vitamin B2, Vitamin B3, Vitamin B5, Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, Vitamin K.

Minerals are selected from: Aluminium (Al), Antimony (Sb), Arsenic (As), Barium (Ba), Beryllium (Be), Bismuth (Bi), Boron (B), Bromine (Br), Cadmium (Cd), Calcium (Ca), Caesium (Cs), Chloride (Cl), Chromium (Cr), Cobalt (Co), Copper (Cu), Cyanide (Cn), Fluoride (Fl), Gallium (Ga), Germanium (Ge), Gold (Au), Indium (In), Iodine (I), Iron (Fe), Lead (Pb), Lithium (Li), Magnesium (Mg), Manganese (Mn), Molybdenum (Mo), Nickel (Ni), Niobium (Nb), Phosphorus (P), Platinum (Pt), Potassium (K), Rubidium (Rb), Scandium (Sc), Selenium (Se), Silicon (Si), Silver (Ag), Sodium (Na), Strontium (Sr), Sulphur (S), Tellurium (Te), Thallium (Ti), Tin (Sn), Titanium (Ti), Tungsten (W), Vanadium (V), Zinc (Zn), Zirconium (Zr). The preferable minerals are: calcium, magnesium, potassium, selenium and zinc. The preferable natural source of minerals and trace elements are herbal extracts and mumijo (mumie-other spelling), natural resin (RU2124887). The EU RDA and proven safe level with daily intake will guard manufactures to the amount of vitamins and minerals per individual dose.

The compositions are, furthermore, applicable for, but not restricted to, oral or nasal, buccal, pulmonary, transdermal and rectal routes of administration. Suitable, but not limiting administration forms are nasal or oral sprays, buccal sprays, chewing

gums, tablets, lozenges, transdermal or buccal patches, nasal gels, transdermal or buccal gels, transdermal or buccal adhesives, or sprays or aerosols for administration to the lungs.

As solid compositions for oral administration, tablets, chewing gum, pills, powders (gelatine capsules, wafer capsules) or granules may be used. In these compositions, the active principle according to the invention is mixed with one or more inert diluents such as starch, cellulose, sucrose, lactose or silica. These compositions can also comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talk, a colouring, a coating or flavouring.

As liquid composition for oral administration, pharmaceutically acceptable solutions, emulsions, suspensions, syrups and elixirs may be used, containing inert diluents such as water, ethanol, glycerol, vegetable oils or liquid paraffin. This composition can comprise substances other than diluents, for example sweetening, thickening, flavouring or stabilising products. Liquid composition may be sterilized for parenteral administration.

The compositions for rectal administration are suppositories or rectal capsules which contain, besides the active products (caffeine, vitamins and/or minerals), excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

The composition for topical administration can be, for example, creams, lotion, mouthwashes, nasal drops or aerosols.

The preferable administration forms are nasal or oral sprays or transdermal patches, as caffeine, vitamins and/or minerals then avoid the hepatic first-pass effect and may be used in smaller doses. Besides the active products, these compositions may also contain diluents, stabilisers, flavouring, acidity regulators, preservatives, aromatic products.

Compositions may be used for manufacture of medicaments and also nutritional supplements, as all active ingredients are 'over the counter' (OTC) products.

The doses depend on the effect sought, the treatment period and the administration route used, they are generally for caffeine between 10 - 300 mg/ daily for an adult and according to the EU RDA for vitamins and/or minerals.

The examples, which follow, illustrate some medicaments according to the invention:

**Example A**

Sachet with composition in the powder form:

Caffeine Citrate	50 mg
Thiamine (B1)	12 mg
Pyridoxine (B6)	50 mg
Sodium bicarbonate	100 mg
Dextrose monohydrate	up to 3g

Contents to be dissolve in the water before use. Maximum recommended amount – 4 sachets per day.

**Example B**

Oral spray (30 ml) with standard dose volume 0.3 ml:

Caffeine Citrate	20 mg/per single dose
Microcrystalline cellulose	5 mg
Sodium chloride	9mg
Thiamine (B1)	5mg
Pyridoxine (B6)	20 mg
Mumijo	30% solution

Single dose will provide: caffeine 20 mg, Vitamin B1- 5mg, Vitamin B6- 20 mg.

Maximum recommended amount – 8-10 sprays per day.

**Example C**

Hard gelatine capsules are manufacturing according to the usual technique:

Caffeine Citrate	50 mg
Thiamine (B1)	12 mg
Pyridoxine (B6)	50 mg
Cellulose	18 mg
Lactose	55 mg
Colloidal silica	1 mg
Sodium carboxymethylstarch	10 mg
Talc	10 mg
Magnesium stearate	1 mg

Maximum recommended amount – 4 capsules per day.



**Claims:**

1. A method and pharmaceutical compositions for effecting withdrawal symptoms or adding in cessation or lessening of caffeine use or substance abuse, and balancing of nutritional deficiency, which developed due to the caffeine abuse.
2. A method of preparing compositions, according to Claim 1, for effecting withdrawal symptoms to caffeine and products containing this chemical, which comprises: combining caffeine, caffeine derivative, or a pharmaceutically acceptable salts with vitamins and/or minerals, chemical or natural in origin, in pharmaceutically acceptable carrier, excipients or agent.
3. The pharmaceutical compositions according to Claim 2, wherein said chemical is caffeine, caffeine derivative, or pharmaceutically acceptable salts thereof.
4. The pharmaceutical composition according to Claim 2, wherein said vitamins are selected from: Bioflavonoids, Biotin, Choline, Folic acid, Inositol, Vitamin A, Vitamin B1, Vitamin B2, Vitamin B3, Vitamin B5, Vitamin B6, Vitamin B12, Vitamin C, Vitamin D, Vitamin E, Vitamin K.
5. The pharmaceutical composition, according to Claim 2, wherein minerals are selected from: Aluminium (Al), Antimony (Sb), Arsenic (As), Barium (Ba), Beryllium (Be), Bismuth (Bi), Boron (B), Bromine (Br), Cadmium (Cd), Calcium (Ca), Caesium (Cs), Chloride (Cl), Chromium (Cr), Cobalt (Co), Copper (Cu), Cyanide (Cn), Fluoride (Fl), Gallium (Ga), Germanium (Ge), Gold (Au), Indium (In), Iodine (I), Iron (Fe), Lead (Pb), Lithium (Li), Magnesium (Mg), Manganese (Mn), Molybdenum (Mo), Nickel (Ni), Niobium (Nb), Phosphorus (P), Platinum (Pt), Potassium (K), Rubidium (Rb), Scandium (Sc), Selenium (Se), Silicon (Si), Silver (Ag), Sodium (Na), Strontium (Sr), Sulphur (S), Tellurium (Te), Thallium (Ti), Tin (Sn), Titanium (Ti), Tungsten (W), Vanadium (V), Zinc (Zn), Zirconium (Zr).
6. A method, according to Claim 1, wherein caffeine, caffeine derivative, or pharmaceutically acceptable salts with vitamins and/or minerals are administered substantially simultaneously at times when a person experiences any withdrawal symptoms.



INVESTOR IN PEOPLE

Application No: GB 0202812.4  
Claims searched: 1-6

Examiner: Dr William Thomson  
Date of search: 22 July 2002

**Patents Act 1977**  
**Search Report under Section 17**

**Databases searched:**

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Other: ONLINE: BIOSIS, CAS-ONLINE, EPODOC, JAPIO, MEDLINE, TXTE & WPI

**Documents considered to be relevant:**

Category	Identity of document and relevant passage	Relevant to claims
X	WO 00/62812A1 (ADVOCARE INTERNATIONAL LLC) See whole document, in particular Example 1 and claims 1-18	1-6
X	US 2001/0055645 (FLOOK ET AL) See whole document, in particular paragraphs [0019]-[0021] and claims 1-20	1-6
X	US 5480657 (ALLEN) See whole document, in particular column 9, lines 1-10, Example 2 and claims 1-9	1-6
X	US 4778677 (EBBESEN) See whole document, in particular Examples I-IV and claims 1-11	1-6
X	WPI Abstract Accession No 2001-406520/43 & RU 2167655 (M.G. CHUKHROVA ET AL) See abstract	1-6

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.